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ONCOLOGY

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Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis

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Abstract Radioembolization with yttrium-90 microspheres (^{90}Y-RE), either glass- or resin-based, is increasingly applied in patients with unresectable liver malignancies. Clinical results are promising but overall response and survival are not yet known. Therefore a meta-analysis on tumor response and survival in patients who underwent ^{90}Y-RE was conducted. Based on an extensive literature search, six groups were formed. Determinants were cancer type, microsphere type, chemotherapy protocol used, and stage (deployment in first-line or as salvage therapy). For colorectal liver metastases (mCRC), in a salvage setting, response was 79% for ^{90}Y-RE combined with 5-fluorouracil/leucovorin (5-FU/LV), and 79% when combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and in a first-line setting 91% and 91%, respectively. For hepatocellular carcinoma (HCC), response was 89% for resin microspheres and 78% for glass microspheres. No statistical method is available to assess median survival based on data presented in the literature. In mCRC, ^{90}Y-RE delivers high response rates, especially if used neoadjuvant to chemotherapy. In HCC, ^{90}Y-RE with resin microspheres is significantly more effective than ^{90}Y-RE with glass microspheres. The impact on survival will become known only when the results of phase III studies are published.

Keywords Yttrium-90 · Radioembolization · Colorectal · HCC · Meta-analysis

Introduction

Internal radiation therapy through transarterial delivery of beta-emitting yttrium-90 (^{90}Y)-loaded microspheres, often referred to as ^{90}Y radioembolization (^{90}Y-RE), is an emerging technique for the treatment of patients with unresectable primary or metastatic liver tumors [1, 2]. The efficacy of this radioembolization technique is based on the fact that intrahepatic malignancies derive their blood supply almost entirely from the hepatic artery, as opposed to the normal liver, which mainly depends on the portal vein for its blood supply [3]. The microspheres are injected selectively into the proper hepatic artery and subsequently become lodged in the microvasculature surrounding the tumor. Very high irradiation doses are delivered to the tumors, whereas the surrounding liver parenchyma is largely spared [4].

Two FDA-approved ^{90}Y microsphere products are in clinical use at present: TheraSphere® (MDS Nordion Inc., Kanata, Ontario, Canada), which are glass microspheres, and the resin-based SIR-Spheres® (SIRTeX Medical Ltd., Sydney, New South Wales, Australia) (Table 1). The glass microspheres are approved for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with hepatocellular carcinoma (HCC). The resin microspheres have FDA premarket approval for the treatment of hepatic metastatic colorectal cancer (mCRC), with adjuvant hepatic arterial infusion of floxuridine. However,

Table 1 Yttrium-90 microsphere products characteristics

Microsphere product	Yttrium-90 characteristics				Matrix material	Density (g/ml)	Diameter (μm)	Administered amount of particles (mg)	Administered number of particles	Standard dose (MBq)	Activity per microsphere (Bq)
	$T_{1/2}$ (h)	Cross section[a] (barn)	β^- energy (keV)	Mean tissue range (mm)							
TheraSphere® (MDS Nordion Inc.)	64.0	1.3	2,280 (99.9%)	3.9	Glass	3.3	25±10	110[b]	4,000,000	5,000	1,250[b]–2,500
SIR-Spheres® (SIRTeX Ltd.)					Resin	1.6	32±10	1,370[b]	50,000,000	3,000	50[b]

[a]Thermal neutron cross section of yttrium-89
[b]Calculated values

patients suffering from other liver dominant cancers have also undergone therapy with these ^{90}Y microspheres. These include, among others, liver metastases of breast cancer, pancreatic cancer, and neuroendocrine tumors [5, 6]. Since in most studies that have been published the majority of patients underwent ^{90}Y-RE in a salvage setting, and most of the literature comprised phase I and II studies with small patient numbers, the overall response and real impact on survival are not known. In order to assess the effect of ^{90}Y-RE for primary and secondary liver malignancies, a systematic meta-analysis has been performed of the available literature.

Methods

Identification of studies

A comprehensive search was carried out using several databases in order to identify relevant studies from 1986 onwards. The following search strategy was used to search the MEDLINE database with PubMed: ("yttrium" [MeSH Terms] OR yttrium [Text Word]) AND ("liver" [MeSH Terms] OR liver [Text Word]). The limit "humans" was used. The EMBASE database was searched with the limit human using: ("yttrium"/exp OR "yttrium") AND ("liver"/exp OR "liver"). The Cochrane library database was searched with the keywords "yttrium" and "liver". The search was completed by searching the reference lists and related articles of all relevant articles found. In addition, the reference lists of two presentations given at a workshop held in Chicago 4–5 May 2007 [7] and the list of publications in the clinicians' section of the webpage of SIRTeX Medical Ltd. [8] and the Resource Library on the webpage of MDS Nordion Inc. [9] were screened.

Inclusion and exclusion criteria

All abstracts of relevant studies were reviewed with a set of predefined inclusion and exclusion criteria. All articles from 1986 onwards which presented data concerning tumor response or survival of patients with primary or secondary liver malignancies after treatment with ^{90}Y glass or ^{90}Y resin microspheres were included for further data extraction. This resulted in 44 articles (Fig. 1). Articles written in a language other than English or German were excluded; articles that presented data that were thought to have been presented previously were used once. Consequently, one article was excluded because it was written in Chinese, and another was excluded, since it was thought to present data that were also presented in another larger trial. This resulted in 42 articles from which data were extracted.

Data extraction

After the initial assessment for inclusion the following data were extracted from the 42 articles selected: study design, number, and demographic data of patients; minor extrahepatic disease included/excluded, previous therapies targeted on the liver tumor, administered dosage, site of microsphere delivery, use of angiotensin II, number of microsphere treatments, (neo)adjuvant therapies, tumor response measured by CT, MRI, and/or ^{18}F-FDG-PET, serum markers measurements (CEA, AFP), time to progression, and survival.

After initial data extraction, the exclusion criteria were reassessed. It became clear that most studies presented adequate data on patients with HCC or with mCRC, and that response was usually measured by CT. The meta-analysis was therefore limited to these two tumor types. In order to perform a meta-analysis, additional exclusion criteria were incorporated. Articles that did not present data about HCC and/or mCRC and articles only presenting data on groups with mixed primary disease were excluded from the meta-analysis. Articles that did not present tumor response measured by CT scans or that did not present data on median survival times were also excluded. Following the additional exclusion criteria, an additional 12 articles were excluded from the meta-analysis.

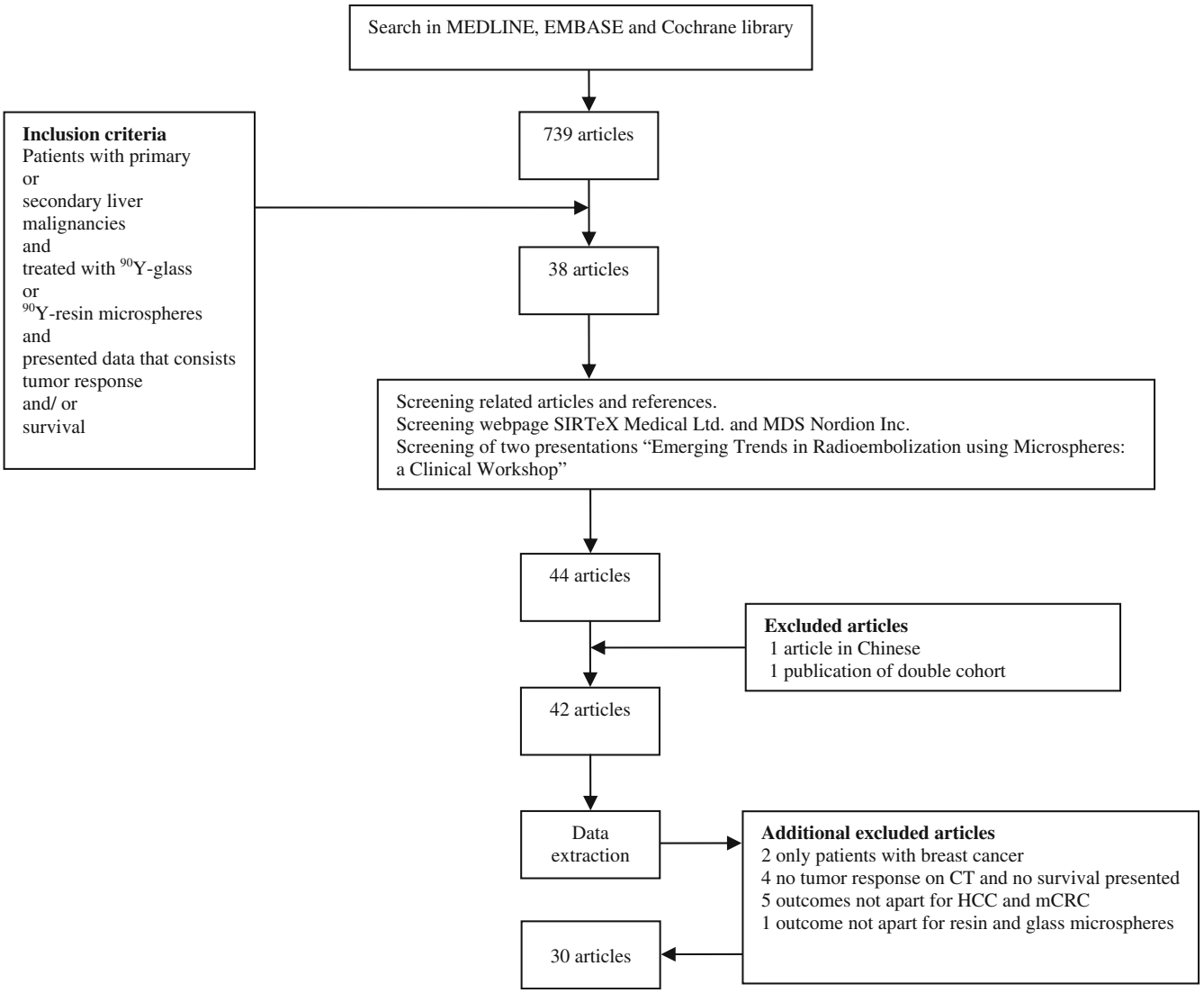

Fig. 1 Flowchart summarizing the selection of relevant articles

Data structuring

The 30 remaining articles were divided into two groups, according to tumor type, i.e., mCRC or HCC. The pathology of these two types of liver tumors is very different. Colorectal carcinoma initially metastasizes to one or a few focal parts of the liver, whereas HCC usually spreads diffusely throughout the liver. Response to chemotherapy is also very different in these tumor types. This resulted in the formation of two groups (mCRC and HCC), for which the studies were compared on design and patient population, in order to assess the comparability of the results.

In the group of patients with mCRC, after data extraction the use of different (generations of) chemotherapy regimens was identified as a major source of heterogeneity. Two covariates were therefore included in the meta-regression model: (1) whether the older generation of cytostatic agents (5-FU/LV or floxuridine) or the newer generation (5-FU/LV + oxaliplatin (FOLFOX) or 5-FU/LV + irinotecan (FOLFIRI)) was used, and (2) whether ^{90}Y-RE was given as a salvage therapy or as a first-line treatment with adjuvant chemotherapy. No separation was made between the microsphere product that was used (glass or resin), because of the small number of patients with mCRC treated with the glass microspheres (ca. 8%).

In view of the chemoresistant nature of HCC [10], previously given therapy was not observed as a source of heterogeneity. Therefore, the main source of heterogeneity observed in this group was the microsphere product used, either glass or resin. This resulted in the formation of two subgroups.

To allow comparability of results with regard to tumor response, the category of 'any response' (AR) was

introduced. The AR category comprises all patients originally from the categories complete response, partial response, and stable disease.

Meta-analysis

The study of Andrews et al. [11] included just one HCC patient. This patient was therefore not included in the analysis. The proportions of patients with AR were modeled by a meta-regression analysis according to Hamza et al. [12]. This method uses the exact binomial likelihood approach instead of an approximate method based on the normal distribution of within-study variability. A random effects model was applied since considerable heterogeneity was observed between the studies. The meta-regression analysis was performed using PROC NLMIXED in SAS version 9.1 as described by Hamza et al.

Results

Thirty articles were included in the meta-analysis. In 999 out of 1,217 patients, tumor response was assessed by CT. The proportion of AR for HCC and mCRC combined varied between 0.29 and 1.00 with a median value of 0.82. Treatment with glass microspheres showed a lower response (AR=0.77) than treatment with resin microspheres (AR=0.85) (p=0.07), with an estimated odds ratio of 0.56 (95% CI 0.29–1.06).

Colorectal liver metastases

In a total of 19 eligible studies 792 patients with mCRC had undergone ^{90}Y-RE [6, 11, 13–29]. In 18 studies tumor response was assessed in a total of 681 patients. Of these patients 486/681 had received ^{90}Y-RE in a salvage setting, of which 124/486 had been previously treated and/or co-treated with 5-FU/LV or floxuridine, and 362/486 had been given the newer-generation cytostatic agents. One hundred and ninety-five patients had received ^{90}Y-RE as a first-line treatment, of which 175/195 were treated with adjuvant 5-FU/LV or floxuridine and 20/195 with FOLFOX.

The specific cytostatic agent(s) ("old" versus "new") that were used did not affect response (p=0.96). Whether ^{90}Y-RE was offered in a salvage setting or as a first-line therapy affected tumor response significantly (p=0.07). The estimated proportions of AR, based on the regression model, were 0.79 and 0.79 in salvage setting and 0.91 and 0.91 in the first-line, for the older and newer chemotherapy, respectively.

Median survival after ^{90}Y-RE, irrespective of differences in determinants (microspheres type, chemotherapy protocol, and stage: salvage or first-line), varied from 6.7 to 17.0 months. The reported median survival from diagnosis of mCRC ranged from 10.8 to 29.4 months (Table 2).

Two randomized controlled trials were performed in patients with unresectable mCRC. In 2001, Gray et al. presented the results for 76 patients who had been randomized to either ^{90}Y-RE (resin) as neoadjuvant to hepatic arterial infusion (HAI) of floxuridine or to HAI alone [14]. Patients in the combination arm showed a significantly greater response when measured by tumor volume, and a significantly increased time to progression. AR was 78% and 59% (p=0.03) for the combination arm and the HAI-alone arm, respectively, and time to progression, based on tumor area measurements, was 15.9 months vs. 9.7 months (p=0.001), respectively. In 2004, Van Hazel et al. reported on the outcome in 21 previously untreated patients with mCRC [15] in a similar study, in which it was demonstrated that the addition of a single administration of resin microspheres prior to 5-FU/LV significantly increased response, time to progression, and survival. In this phase II trial AR was 100% in the combination arm vs. 60% in the chemotherapy-alone arm (p<0.001), time to progression 18.6 and 3.6 months (p<0.0005), respectively, and survival 29.4 and 12.8 months (p=0.02). Thirty-six months postrandomization 36% of patients in the combination arm were still alive, whereas no patients from the 5-FU/LV-alone arm were alive at that time.

Hepatocellular carcinoma

In 14 articles clinical data were presented on tumor response and survival for 425 patients with HCC who had received ^{90}Y-RE [11, 18, 24, 30–40]. Twelve studies presented data of tumor response for a total of 318 patients. Treatment with resin microspheres was associated with a significantly higher proportion of AR than glass microsphere treatment (0.89 vs. 0.78 (p=0.02)).

Median survival was reported in seven studies in which survival time was defined as survival from treatment or from diagnosis or recurrence. Median survival from microsphere treatment varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4–24.0 months (Table 3).

Discussion

This meta-analysis showed that in patients with mCRC the tumor response of ^{90}Y-RE is high, with AR rates of approximately 80% in a salvage setting, and over 90% when used as first-line treatment, as neoadjuvant to chemotherapy. The response rates reported for studies in which 5FU/LV was combined with irinotecan or oxaliplatin were similar to those of studies in which only 5FU/LV was used. This can probably be explained by differences in the criteria for tumor response that were used (WHO versus RECIST criteria [41]).

Regarding the question as to which microsphere is most effective in the treatment of mCRC—glass or resin—no

Table 2 Tumor responses and median survivals after ^{90}Y-RE in mCRC

Study	Number (*n*)	Results									
		Tumor response on CT								Median survival (months)	
		CT performed in	Response measured at (months post ^{90}Y-RE)	RECIST[a]	CR (%)	PR (%)	SD (%)	AR (%)	PD (%)	From diagnosis	From ^{90}Y-RE
Resin microspheres											
Gray et al. (1992) [13]	29	22	3	–	0	45	37	82	18	NR	NR
Stubbs et al. (1999) [29]	30	27	3	–	0	70	19	89	11	10.8 (range 1.9–41.0)	6.7 (range 1.0–15.8)
Gray et al. (2000) [28]	71	51	3	–	0	75	12	86	14	17.3	9.9
Gray et al. (2001)[b] [14]	36	36[c]	3	–	6	44	28	78	14	NR	17.0
Stubbs et al. (2001) [16]	50	44	3	–	0	73	18	91	9	14.5 (range 1.9–91.4)	9.8 (range 1.0–30.3)
Van Hazel et al. (2004)[b] [15]	11	11	3	Yes	0	91	9	100	0	29.4	NR
Lim et al. (2005) [18]	30	30	2	Yes	0	33	27	60	40	NR	NR
Lim et al. (2005) [19]	32	32	2	Yes	0	31	28	59	41	NR	NR
Murthy et al. (2005) [17]	12	9	NR	Yes	0	0	56	56	44	24.6	4.5
Mancini et al. (2006) [20]	35	35	1.5	Yes	0	12	76	88	13	NR	NR
Kennedy et al. (2006) [21]	208	208	3	–	0	36	55	91	10	NR	Responders 10.5 Non-responders 4.5
Stubbs et al. (2006) [22]	100	80	3	–	1	73	20	94	6	16.2 (range 1.1–101.6)	11 (range 0.1–76.6)
Jakobs et al. (2007) [24]	18	18	2–3	–	0	NS	NS	76	24	NR	NR
Sharma et al. (2007) [23]	20	20	3	Yes	0	90	10	100	0	NR	NR
Glass microspheres											
Anderson et al. (1992) [25]	7	7	2	–	0	0	86	86	14	NR	11 (range 5–25+)
Andrews et al. (1994) [11]	17	17	2	–	0	29	29	59	41	NR	13.8
Wong et al. (2002) [26]	8	8	3	–	12	12	38	63	38	NR	NR
Lewandowski et al. (2005) [27]	27	26	3	–	0	35	52	87	13	NR	9.3 (95% CI 7.2–13.3)
Sato et al. (2008) [6]	51	51	5.3	–	NR	NR	NR	NR	NR	NR	15.2

CR complete response, *PR* partial response, *SD* stable disease, *AR* any response (= CR + PR + SD), *PD* progressive disease, *NR* not reported, *NS* not specified

[a]Response measured and presented according to RECIST criteria [41]

[b]Response and survival for ^{90}Y-RE arm alone

[c]CT of 3 out of 36 patients not assessable

conclusions can be reached since only 8% of the patients with mCRC were treated with the glass microspheres. Furthermore, the meta-analysis showed that resin microspheres were significantly more effective in treating HCC than glass microspheres (AR 89% vs. 78% (p=0.02)). This is a rather unexpected finding, because only the glass microspheres are FDA-approved for treating HCC, whereas the resin microspheres are approved for mCRC, not HCC. It may be postulated that this outcome is the consequence of the substantial difference in numbers of microspheres that are infused: a dose of glass microspheres consists of 4 million microspheres, whereas a dose of resin microspheres usually contains 50 million microspheres [42]. It has been reported in the literature that administration of resin microspheres had to be prematurely halted, before the predetermined amount of radioactivity was instilled, due to macroscopic embolization [43]. In contrast, the relatively very low number of glass microspheres per dose is associated with microscopic embolization [39]. However, the low number of particles infused in the case of the glass microspheres may be a disadvantage when targeting a tumor type that is often diffusely spread throughout the liver at the time of diagnosis [44]; the radiation dose would be distributed in and around the tumors too heterogeneously to be able to deliver a tumoricidal dose to the entire lesion even if the total

Table 3 Tumor responses and median survivals after ^{90}Y-RE in HCC

Study	Number (*n*)	Results									
		Tumor response on CT								Median survival (months)	
		CT performed in	Response measured at (months post ^{90}Y-RE)	RECIST[a]	CR (%)	PR (%)	SD (%)	AR (%)	PD (%)	From diagnosis (or reoccurrence)	From ^{90}Y-RE
Resin microspheres											
Lau et al. (1994) [31]	18	18	2	–	0	44	44	89	11	NR	7.1
Lau et al. (1998) [32]	71	71	2	–	0	27	65	92	8	9.4 (range 1.8–46.4)	NR
Lim et al. (2005) [19]	5	4	2	Yes	0	25	50	75	25	NR	NR
Sangro et al. (2006) [33]	24	21	2	–	NS	NS	NS	88	12	NR	7.1 (95% CI 2.1–12)
Jakobs et al. (2007) [24]	5	5	2–3	Yes	0	NS	NS	100	0	NR	NR
Glass microspheres											
Houle et al. (1989) [34]	7	7	NR	–	0	0	29	29	71	NR	NR
Andrews et al. (1994) [11]	1	1	2	–	0	0	0	0	100	NR	NR
Dancey et al. (2000) [35]	22	19	2–3	–	5	16	58	79	21	NR	12 (range 2–42)
Carr et al. (2004) [36]	65	65	3	–	3	28	40	71	29	Okuda I 12 (95% CI 2–42) Okuda II 10 (95% CI 6–20)	NR
Geschwind et al. (2004) [30]	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	Okuda I 21.0 Okuda II 1.0
Liu et al. (2004) [37]	11	11	1–1.5	–	9	72	0	82	18	NR	NR
Salem et al. (2005) [38]	43	43	Varying	–	NS	NS	NS	79	21	Okuda I 24 (95% CI 18–28) Okuda II 12 (95% CI 9–17)	NR
Kulik et al. (2006) [40]	35	34	6 (0.8–16)	–	NS	NS	NS	88	12	NR	NR
Sato et al. (2006) [39]	19	19	5 (1.5–14)	–	NS	NS	NS	79	21	NR	NR

CR complete response, *PR* partial response, *SD* stable disease, *AR* any response (= CR + PR + SD), *PD* progressive disease, *NR* not reported, *NS* not specified

[a]Response measured and presented according to RECIST criteria [41]

amount of radioactivity of a dose of glass microspheres is at least 50% higher than is the case in the resin microspheres (Table 1). Another (theoretical) consideration is that the macroembolic effect of the resin microspheres is accompanied by a greater lack of oxygen resulting in ischemia and therefore enhanced efficacy. On the other hand, shortage of oxygen might also diminish the tumoricidal effect of ionizing radiation due to a lack of oxygen radicals that is produced in this environment.

However, this macroembolic effect can be associated with clinical signs, the so-called postembolization syndrome (PES), which is reported to frequently occur following resin microspheres infusion, but not often subsequent to administration of the minimally embolic glass microspheres. PES is characterized by fatigue, nausea, fever, right upper quadrant pain, and/or vomitus, all of which are transitory and can be effectively controlled by outpatient medication [21, 39, 45–47].

Serious complications have been reported when microspheres were inadvertently deposited in excessive amounts in organs other than the liver. Conditions that have been reported include gastrointestinal ulceration/bleeding, gastritis/duodenitis, cholecystitis, pancreatitis, and radiation pneumonitis [42, 45, 48–52]. Training, careful patient selection, meticulous pretreatment assessment, and coiling of relevant vasculature reduce complication rates massively [53]. Radiation-induced liver disease following ^{90}Y-RE has been reported sporadically [15, 54]. Careful patient selection and individualized dose calculation minimize the risk of this complication. Profound and persistent lympho-

penia, with rapid onset and in some cases lasting over 12 months, though without clinical consequences, has been reported in patients with HCC following ^{90}Y-RE with glass microspheres [36, 38]. This complication has not been observed subsequent to ^{90}Y-RE with resin microspheres (as monotherapy). The underlying mechanism is not clear but myelosuppression is not probable since leaching of radioactivity from the glass microspheres does not take place [55]. However, following ^{90}Y-RE, in addition to the liver tumors and to some extent the liver parenchyma, a radiation dose is delivered to the blood each time it passes the liver, which might explain this adverse laboratory event.

Unfortunately, in this meta-analysis overall tumor response could only be assessed as 'any response', which is caused by the reality that response categories were not uniformly defined in the analyzed studies. It is expected that this problem of being able to compare tumor response will disappear in the near future, since the RECIST criteria, published in 2001 [41], are evermore applied. In accordance with the RECIST criteria, tumor response in malignant liver disease is assessed using cross-sectional anatomic imaging (CT, MRI), by measuring tumor size. However, lesion size reduction does not always occur even if treatment is effective. This is associated with different peri- and endotumoral processes that can occur post ^{90}Y-RE, e.g., peritumoral edema and hemorrhage, and ring enhancement [56]. Therefore, actual tumor response may often be better than is reported, based on CT measurements alone. In a significant number of cases 'stable disease' could actually be minor, partial, or even complete response. In order to improve sensitivity in assessing tumor response, it is therefore strongly recommended that ^{18}F-FDG-PET or functional MRI (diffusion-weighted MRI) is added to post-treatment response assessment protocols [56–59].

Only two randomized controlled trials were found in the literature, both on resin microspheres and mCRC. The results were encouraging, showing a major survival benefit for the ^{90}Y-RE + chemo arm. However, since then larger controlled trials have commenced, in which more effective chemotherapeutics were used [60].

In this paper the emphasis was placed on ^{90}Y-RE in patients with unresectable HCC and mCRC. Nonetheless, patients with liver metastases from primaries other than mCRC have been treated with ^{90}Y-RE. This is particularly the case for liver metastasized breast cancer, of which response rates of over 90% are reported [61, 62]. ^{90}Y-RE has been applied in patients with neuroendocrine liver metastases, too, albeit in small numbers [11, 63]. Reported response rates were 100%, and it would therefore be worthwhile to further explore the use of ^{90}Y-RE for this indication.

Fortunately, ^{90}Y-RE is not the only novel and effective treatment option offered to patients with unresectable HCC. Recently, a breakthrough has been reported in the field of biological agents. For sorafenib (Nexavar®, Bayer Healtcare AG, Leverkusen, Germany), an oral multikinase inhibitor, a statistically significant and clinically meaningful improvement in survival has been shown in HCC patients with advanced disease: 10.7 months in the sorafenib group versus 7.9 months in the placebo group (p=0.0006) [64]. Recently, a phase I/II trial has started in which patients with unresectable HCC are treated with the resin microspheres plus sorafenib [60].

The clinical efficacy of other promising molecular agents, e.g., bevacizumab, erlotinib, is currently being investigated as well. When added to FOLFOX or XELOX (capecitabine + oxaliplatin), the angiogenesis inhibitor bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA, USA) has been proven to prolong survival of patients with colorectal cancer by approximately 6 months compared with FOLFOX or XELOX alone [65, 66]. In fact, in an ongoing multicenter study, the "FAST" trial, patients with unresectable colorectal liver metastases are treated concurrently with FOLFOX or FOLFIRI, bevacizumab, and ^{90}Y-RE (resin microspheres) [67].

In conclusion, ^{90}Y-RE is associated with high response rates, both in a salvage and in a first-line setting. The true impact on survival will only become known after publication of several ongoing and/or to be initiated phase III studies. The results of trials in which ^{90}Y-RE and modern chemotherapy agents are combined with novel biological agents are awaited with interest as well.

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